Restriction Requirement

The Examiner has maintained the restriction of the application into seven groups of claims. Applicants respectfully submit that such a division of the claims is improper and again request rejoinder of at least groups I, III, IV and V for examination in the present application.

Applicants have previously argued that the Examiner fails to carry his burden of showing that the restricted claims constitute an "independent and distinct" invention. 35 U.S.C. § 121. It is not enough that the invention merely be distinct. A fragment of a gene, though distinct, cannot be considered an invention independent of the full length gene. Furthermore, an embodiment that is "less than" its principal embodiment cannot be said to be more burdensome to search than the principal embodiment. As the Examiner fails to establish this additional search burden, the claims of group III should be rejoined with the claims of group I. M.P.E.P. § 803.

Applicants have also previously pointed out that the claims of groups IV and V constitute a process for using the raffinose synthase gene of the invention by hybridization and PCR, respectively. With respect to these claims, the Examiner's basis for dividing the claims does not meet the relevant standard for restriction of a product from a process for its use. The Examiner must show either or both of that (1) the process as claimed can be performed using a materially

different product or (2) the product as claimed can be used in a materially different process. The Examiner has demonstrated neither of these. Accordingly, the claims of groups IV and V should be rejoined for prosecution in the present application.

In addition, Applicants would remind the Examiner of the policy of the USPTO as set forth in M.P.E.P. § 803.04 that up to ten distinct nucleotide sequences shall be examined in a single patent application. Applicants submit that the "gene fragments" of claims 21-23, which the Examiner deems patentably distinct sequences, should nonetheless be examined together with the full-length sequences pursuant to this policy.

For all of the above reasons, Applicants request that the claims of groups I, III, IV and V be joined for examination in the present application.

Sequence Listing and CRF

Applicants submit together with this paper a revised Sequence Listing and new CRF. The revision to the Sequence Listing is addition of an "N" residue at position 1642 of SEQ. ID. NO. 4. The addition of this residue, which represents all four nucleotides, is not new matter, as the Sequence Listing clearly shows the corresponding alanine amino acid in the translation below the nucleotide sequence. At page 16 of the specification, the codon

table shows that alanine is encoded by a codon GC, followed by any of the four nucleotides in the third position. Thus, introduction of "N" as residue 1642 of the nucleotide sequence is appropriate and is not new matter.

The revised Sequence Listing is provided in the format of PATENTIN Version 1.0, in view of the filing of the present application prior to July 1, 1998.

Statement Under 37 C.F.R. § 1.825 (d)

In compliance with 37 C.F.R. 1.825(d), the following Statement is made:

A substitute computer readable form of the revised SEQUENCE LISTING, is submitted herewith.

20-4348.rv2 is a file in Text format which contains the same material as the printed copy of the substitute SEQUENCE LISTING submitted herewith in connection with the present application, but lacks format information.

No new matter is incorporated by the amended Sequence Listing as explained above.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 5, 8 and 29 stand rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to distinctly

claim the subject matter of the invention. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner is basically asserting that the claims are too broad. But, this is not the same as indefiniteness under 35 USC § 112, 2nd paragraph. *In re Gardner* 166 USPQ 138 (CCPA 1970). *See also*, M.P.E.P. 706.03(d). The sections (b) of claims 5 and 8 objected to by the Examiner recite proteins having a variant of a specific amino acid sequence (described in section (a) of the claim) and that has the biological activity of raffinose synthase. Consistent with the definition of "raffinose synthase protein" in the specification (p. 22, lines 22 ff.) claims 5 and 8 recite that the variants are those wherein "one or several" amino acids are added, deleted or substituted. Thus, the term "several" constrains the amino acid sequence. Exhibit 1, a page from a dictionary, shows the definition of "several" to be "more than two or three, but not many." Thus, amino acid sequences within the scope of claims 5 and 8 are those that differ from the sequence recited in part (a) by several amino acids. It is not specified which particular amino acids are changed, deleted or added, but the number of the variations is not large. (Note the definition of "many" also provided in Exhibit 1.)

However, this great structural flexibility is constrained by a functional limitation that the resulting polypeptide must exhibit

raffinose synthase activity. Raffinose synthase activity is defined in the specification by the assay presented in Example 2 beginning on p. 26. One of ordinary skill in the art can easily perform this assay upon any particular polypeptide to determine if it has raffinose synthase activity. Accordingly, it is easy to know if a particular nucleotide sequence, which encodes that polypeptide, infringes claim 5 or 8. Thus, the "metes and bounds" of claims 5 and 8 are clear.

Claim 29 recites a "raffinose synthase gene" obtained by a hybridization process described in claim 21, i.e., by hybridization to a known raffinose synthase gene. The metes and bounds of this claim are also clear. If the polynucleotide one is referring to was isolated by hybridization to a known raffinose synthase gene, or fragment of the known gene, then that polynucleotide falls within the scope of claim 29.

From the above explanation, one can see that the language of the claims is sufficiently definite to allow one of ordinary skill in the art to determine if an activity that they contemplate lies inside or outside the scope of the claim. This is all that is necessary to "distinctly claim the invention" and therefore the rejection of claims 5, 8 and 29 under 35 U.S.C. § 112, second paragraph should be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

Written Description

Claims 1-18 and 29-36 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description of the claimed invention. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner relies heavily upon the holding of *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). Applicants wish to point out at the very beginning that the facts of the present application are very different from the facts in *Lilly*. First, the claim in *Lilly* encompassed all "mammalian" insulin genes, even though the specification only completely described a single gene (encoding rat insulin) and poorly described a process for obtaining additional insulin genes (plating clones, picking them and sequencing them to determine if the cDNA encoded an insulin gene).

In contrast, the present application describes a plurality of raffinose synthase genes (SEQ ID NOS:2, 4, 6 and 8) and furthermore provides description of a method for obtaining a raffinose synthase gene from any desired organism (or at least surveying the organism for the existence of the gene) by performing a PCR reaction with one or more of a number of upstream and downstream primers. Furthermore, at least some of the rejected claims recite that the nucleotide sequence is one that either has a specific nucleotide sequence or

that encodes an amino acid sequence having up to several amino acids added, deleted or changed.

The function of the written description requirement is to assure that the inventor in fact had the claimed invention in his possession at that time the application was filed. *See*, Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement. 63 F.R. 32639 (1998). In the instance of the *Lilly* case, it was clear that at the time the application was filed, the inventors did not possess the invention broadly. They had isolated but a single insulin gene, and that from a rat, an organism that was not really of interest to the pharmaceutical industry, which desires to use human genes and gene products. The broad claim to genes encoding "mammalian" insulin was a bald attempt to extend the limited attainments of the inventors to cover the invention that was of real value.

On the other hand, in the present application the inventors have described four variant cDNAs, obtained from four different plant species, that encode proteins having the desired activity. The inventors have further provided examples of PCR primers and detailed description of how to use them to isolate additional examples of isolated DNA encoding raffinose synthase from other species. Working examples (7 and 9-11) of use of the PCR primers to perform such isolations are provided. This disclosure is much more than a "mere

statement that [broadly claimed DNA] is part of the invention and reference to a potential method of isolating it." *Fiers v. Sugano,* 25 USPQ2d 1601 (Fed. Cir. 1993). This disclosure constitutes actual variants within the claimed genus and actual methods that can be used to find the next species within the genus. Furthermore, the demonstration of isolation of three additional species of cDNA within the scope of the claims, starting from a first one obtained by the inventors, establishes predictability of obtaining additional species.

The inventors have further provided description of an assay that can be used to determine if the protein encoded by any gene isolated by the method of the Example in fact is a functional raffinose synthase. *See*, Example 2 at pp. 26 ff.

Clearly the present application "convey[s] the information that an application has invented the subject matter which is claimed." *Guidelines* at p. 32640. Thus, the rejection of claims 1-18 and 29-36 under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description of the claimed invention, should be withdrawn.

Enablement

Claims 1-5, 7-8, 10-11, 14-16 and 29-36 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enabling disclosure

in the specification. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The factors to be examined in considering enablement are set forth in *Ex Parte Forman*, 230 USPQ 546 (BPAI 1986), and are applied in the instance of a biotechnology invention in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Essentially, the process is to determine the breadth of the claims, then to balance the disclosure of the specification together with what is known at the time of its filing by one of ordinary skill in the art against the unpredictability of the art. Then, the balance is examined in light of the scope of the claims. When the weighing finds that the disclosure and prior art overcome the unpredictability, a broad claim is allowable.

The point of the examination is to determine if undue experimentation is necessary to practice the invention throughout the scope of the challenged claim. The amount of experimentation is not determinative. If the art expects a large amount of experimentation to be performed to accomplish certain aspects of the claimed invention, this is acceptable, provided that the specification, together with the prior art, describes how to perform the required experimentation. *Wands* at p. 1406.

The Isolated DNA Claims

Claims 1-5, 7-8, 10-11, 14-16 and 29-30 and 32 are directed to cloned DNA encoding raffinose synthase. The Examiner asserts that the present claims encompass all isolated DNA encoding a raffinose synthase protein of a plant, and that the specification does not enable this broad claim. Applicants submit that proper weighing of the factors in the present case will show that enablement outweighs unpredictability and thus broad claims are indeed enabled.

1. The Scope of the Claims

Applicants acknowledge that the claims are broad in scope.

2. Disclosure of the Specification and What is Known in the Art

The disclosure of the specification is described in detail above in arguments against the written description rejection. In essence the specification discloses two specific nucleotide sequences encoding complete raffinose synthase proteins, a number of sets of primers that can be used to isolate additional species of nucleic acids encoding raffinose synthase by a PCR and an assay for determining the raffinose synthase activity of any protein expressed by an isolated nucleic acid or its presence in crude extracts of any particular plant. The latter is especially useful for screening plant tissues to determine if a raffinose synthase is expressed by

the plant and therefore whether isolation of a cDNA from that plant should be attempted by the methods disclosed in the specification.

With respect to what is known in the art, Applicants submit that the prior art provides methods for random, saturating mutagenesis of any isolated DNA so as to provide a large library of variants of any starting sequence. The prior art also provides the expectation that any such library would have to be screened to determine if any individual clone would encode an active enzyme. As noted above, this expectation removes the requirement for screening from that category of experimentation considered undue.

The Examiner also should consider that the specification discloses methods for purifying raffinose synthase and for expressing raffinose synthase as a fusion protein from cloned DNA. The specification further discloses methods for producing antibodies from the isolated protein and, together with the prior art, this disclosure enables the creation of an immunological screen for host cells expressing raffinose synthase. Such an immunological screen can be performed in a high-throughput manner.

3. The Unpredictability of the Art

Balanced against this thorough disclosure of the specification, the powerful tools provided by the prior art, and the expectation in the art that application of those tools requires a considerable

amount of time and labor, is the "unpredictability" of the art of biotechnology.

The Examiner is essentially asserting that it is unpredictable what specific sequence a cloned DNA according to the claims might have. But, this is not the correct level at which to examine unpredictability. In fact, it is predictable that, by mutagenizing one of the four specific sequences disclosed in the specification and screening a library of mutants, one of ordinary skill in the art could obtain a variant cDNA encoding a protein having raffinose synthase activity. *See, Wands* at p. 1406, 1407. It is also predictable that one of ordinary skill in the art could isolate genomic or cDNA from any plant that has a gene for raffinose synthase, and by using the primers disclosed in the specification, could obtain isolated DNA encoding that raffinose synthase species. The specification establishes this predictability by providing three working examples of accomplishment of exactly that task.

4. Conclusion

Applicants submit that the Examiner's assertion of unpredictability in the art of cloning DNA encoding a particular enzyme activity, when the invention provides one or more species of the desired DNA and an assay for the desired activity, is unfounded. Thus, unpredictability in the art is low. On the other hand, the

specification, together with the prior art, provide an expectation that substantial experimentation is needed to practice the invention broadly and also provide a large amount of guidance as to how that experimentation should be conducted. Thus, the knowledge of the practitioner is high. Weighing the knowledge of the practitioner against the unpredictability of the art, one finds that the practitioner is able to practice the invention broadly. Comparing the scope of the claims to this ability, one finds them commensurate. Accordingly, the rejection of 1-5, 7-8, 10-11, 14-16, 29-30 and 32 under 35 U.S.C. § 112, first paragraph, for alleged lack of enabling disclosure in the specification, should be withdrawn.

The Transformed Host Cell Claims

Claims 31, 33 and 34 are also rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. These claims are directed to host cells transformed with the isolated nucleic acid of the invention. They recite no expression limitations or limitation that the transformed cell is a plant cell. The Examiner does not make any reasoned statement as to why these claims are particularly less enabled than the isolated nucleic acid claims and therefore Applicants' arguments for enablement of the isolated DNA claims and request for withdrawal of the rejection apply to these claims as well.

The Transgenic Plant Claims

Claims 35 and 36 also stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement by the specification. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Claims 35 and 36 either recite that a plant host cell is transformed with isolated nucleic acid of the invention or that the metabolism of a host cell is to be altered by expression of isolated nucleic acid of the invention. In this regard, the Examiner has provided additional reasoned statements as to why the disclosure is not enabling. Thus, Applicants address these claims with additional arguments.

The Examiner's arguments are essentially directed to the unpredictability aspect of the enablement determination. The Examiner proffers the Napoli reference as showing that merely introducing an isolated DNA into a plant, in the sense orientation, does not guarantee that the desired phenotype will actually be expressed. The Carvalho reference is asserted for the same reason. The Ejdeback reference is also asserted to show unpredictability of expression of genes in *E. coli*.

With respect to the Ejdeback reference, and simply accepting the Examiner's characterization of it, Applicants submit that in fact that reference teaches how to overcome problems of expression in *E.*

coli. The reference suggests that the inserted DNA should be engineered to reflect codon usage in that organism and furthermore suggests other modifications to increase mRNA and protein stability, as acknowledged by the Examiner. Thus, the Ejdeback reference in fact supports enablement of the present invention. Furthermore, Applicants have demonstrated expression of cloned raffinose synthase cDNA in *E. coli* in Example 8 of the specification (pp. 33 ff.).

The Napoli and Carvalho references concern expression of genes other than raffinose synthase, and so, as to the presently claimed invention, are rather irrelevant. Applicants suppose that the Examiner is presenting them as evidence of unpredictability of gene expression in plants generally. Applicants address application of the references to each of claims 35 and 36 separately.

Claim 35 does not recite any limitation that the transformed plant cell must express the raffinose synthase. In fact, plant cells in which raffinose synthase expression has been silenced have utility. For example, it is desirable to decrease the amount of raffinose contained in plants eaten by animals, including humans, that cannot digest raffinose. Furthermore, in the production of refined sugar (sucrose) from plants, raffinose is an impurity that inhibits crystallization. Thus, the content of raffinose in plants used for sugar production is preferably minimized.

On the other hand, there are instances when it is desirable to increase the amount of raffinose in a plant. For example, raw material plants used to produce food additives for promoting growth of desirable enterobacteria preferably have increased raffinose content.

Thus, it is seen that, regardless of whether introduction of isolated nucleic acid encoding raffinose synthase results in increased or decreased production of the enzyme, the transformed plant that results have utility. Accordingly, claim 35 must be considered enabled regardless of whether expression of a raffinose synthase transgene is observed or not.

As to claim 36, which does require expression of the transgene, (an also applicable to claim 35 to the extent it encompasses embodiments where the gene is expressed), as explained above, the practitioner of the art expects to have to perform a step of screening any transgenic plant obtained for stable expression of raffinose synthase at the desired level, be it high or low. Methods for making transgenic plants are disclosed and an assay of plant tissue for raffinose synthase activity is described in the specification. Thus, the specification provides disclosure that enables creation of large numbers of transgenic plants in a single experiment and that enables performance of the required screening. One of ordinary skill in the art is provided with the tools to

isolate a transgenic plant having any particular level of raffinose synthase activity and stably expressing that activity. Applicants disagree that stable transmission of the transgene to progeny must be established to show enablement, as first generation transformed plants have utility. However, the above-explained tools can equally be used to assess stable transmission of the raffinose synthase transgene to progeny. Thus, the specification is fully enabling of the invention as described in claims 35 and 36 and the instant rejection should be withdrawn.

Additional Evidence of Enablement

Applicants further submit evidence of enablement of the invention in the form of a Declaration under 37 C.F.R. § 1.132 by Dr. Eijiro Watanabe, one of the co-inventors of the subject matter of the present application. Dr. Watanabe's declaration presents results of experiments in which tobacco plants are transformed with a recombinant vector for expression of the broad-bean raffinose synthase. The expression vector was that made in Example 12 of the specification. Transformed plants were obtained by leaf disc infection, a process known in the prior art (1988), as indicated. Screening for transgenic plants was performed by PCR as known in the art using primers noted in List 14 of the specification (p. 40, SEQ. ID. NOs. 81-84). Raffinose synthase activity was measured in four

transgenic plants as described in the specification in Example 2. All four of the transgenic plants exhibited raffinose synthase activity at least two-fold higher than control, untransformed plants. The data presented by Dr. Watanabe unambiguously demonstrate that one of ordinary skill in the art can practice the transformed plant cell and transgenic plant embodiments of the invention using the teachings of the specification combined with the knowledge and expectations of the prior art. For this additional reason, the rejection of claims 35 and 36 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement by the specification, should be withdrawn.

In view of the above amendments and remarks, the claims remaining in the application, as amended, are asserted to define patentable subject matter. Reconsideration and withdrawal of the standing rejections is requested. Allowance of claims 1-19, 21-36, 40 and 41 is respectfully solicited.

If there are any minor matters precluding allowance of the application that can be resolved by a telephone discussion, the Examiner is invited to contact Mark J. Nuell, Ph.D. (Reg. No. 36,623) at 703-205-8000.

Pursuant to 37 CFR 1.17 and 1.136(a), Applicants petition for an extension of time of three (3) months for filing a response in connection with the present application. The required fee of $870.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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attachments: Exhibit I
Watanabe Declaration
Revised Sequence Listing and CRF